

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

**SUMMARY OF TOXICOLOGY DATA
FENPYROXIMATE (FORMERLY NNI-850)**

Chemical Code # 5784 Tolerance # 52876

SB 950 # N/A

Original date 8/29/01

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	No data gap; no adverse effect

Toxicology one-liners are attached.

All records through 52876-045 179657 were examined. This includes all records indexed by DPR as of 8/29/01.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T187542.doc

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****52876-033 179644** Aughton, P., "NNI-850: Combined oncogenicity and toxicity study by dietary administration to CD rats for 104 weeks", Life Science Research Limited, June 2, 1989. LSR Report No. 89/NHH034/0921. Fifty CD rats/sex/group were dosed in diet at 0, 10, 25, 75, or 150 ppm with Fenpyroximate (formerly called NNI-850) (97.2%) for 2 years in an oncogenicity study. Additional chronic toxicity study rats were dosed at the same levels for 1 year (10/sex/group) or 2 years (20/sex/group). All essential elements of a combined study were included. Estimated mean intakes for oncogenicity study rats were 0.40, 0.97, 3.00, and 6.20 mg/kg/day for males, and 0.49, 1.21, 3.81, and 8.01 mg/kg/day for females. NOEL = 25 ppm (decreased body weights and modestly decreased food consumption in both sexes, and minor decrements in thyroid and liver weights without associated histopathology). Observations which appeared to be treatment-related at 150 ppm included slightly reduced glucose levels and a marginal increase (NS) in uterine stromal endometrial hyperplasia (7/50 vs. 2/50 in controls). Treatment did not elicit neoplasia. Acceptable, with no adverse effect. Aldous, 7/19/01.

CHRONIC TOXICITY, RAT

(There is an acceptable "Combined" rat study)

CHRONIC TOXICITY, DOG

****52876-035 179646** Broadmeadow, A., "NNI-850: toxicity study by oral (capsule) administration to beagle dogs for 52 weeks," Life Science Research Ltd, Eye, Suffolk, England, Aug. 9, 1989. LSR Report No. 89/0802. Four beagles/sex/group were dosed daily by gelatin capsule at 0, 0.5, 1.5, 5.0, or 15 mg/kg/day of fenpyroximate (formerly NNI-850, purity 98.0%) for 52 weeks in a chronic study. No NOEL was established. Cholesterol was reduced below control values at all dose levels in both sexes at week 50. As explained in the review discussion section, these data do not reflect the most important outcome of this study. Rather, a dose-related diarrhea increase in 5-15 mg/kg/day males reflects a functionally more important response. High dose findings in both sexes included diarrhea and EKG changes (bradycardia and slightly reduced p-wave amplitude). Other high dose effects were increased salivation (F) and decreased food consumption with significantly reduced body weight gain (M). One high dose male had such a reduced appetite that it was offered meat supplement to its regular diet for 2 weeks. Afterwards this dog was able to subsist on standard diet, but with a consistently reduced appetite for the next 5 months. This reviewer suggests therefore that 1.5 mg/kg/day represents

a NOEL for functionally important changes. Both bradycardia (a possible adverse effect) and diarrhea plausibly reflect autonomic nervous system effects. Acceptable. Aldous, 7/19/01.

52876-036 179647 Todhunter, J. A., "Supplemental information in regard to MRID 43429503 Guideline 83-1(b): Chronic oral toxicity in the dog". This is a rebuttal to EPA request for a mechanistic study to "explain" organ weight differences in testes, prostate, and epididymides in the dog chronic study, above. Rebuttal shows that there is no organ weight pattern to warrant such a study. No worksheet. Aldous, 6/27/01.

ONCOGENICITY, RAT

(There is an acceptable "Combined" rat study.)

ONCOGENICITY, MOUSE

**52876-034 179645 Shirasu, Y., "NNI-850: 18-month oral oncogenicity study in mice", Institute of Environmental Toxicology, Tokyo, 7/29/89. Report No. IET 87-0036. Fifty SPF ICR (Crj:CD-1) mice/sex/group were dosed in diet with 0, 25, 100, 400, or 800 ppm fenpyroximate (formerly NNI-850) for 18 months in a standard oncogenicity study. Mean dietary intakes were 2.4, 9.5, 38.0, and 69.6 mg/kg/day in males and 2.4, 10.2, 41.4, and 73.1 mg/kg/day in females. NOEL = 25 ppm (substantial, dose-related decrements in body weights and food consumption in both sexes). Ovarian atrophy was slightly but significantly increased in incidence (but not severity) in 400 and 800 ppm females. This was possibly related to reduced food consumption and altered nutritional status, and does not appear to be a pivotal finding. Relative kidney weights were elevated in 400 and 800 ppm females, without histopathology correlates. The majority of statistically significant histopathologic findings at the higher two dose levels were reductions in age-related lesions (including lung carcinomas and liver adenomas in 400 and 800 ppm males). Study is acceptable, with no adverse effects. Aldous, 7/18/01.

REPRODUCTION, RAT

**52876-032 179643 Higgins, C., "NNI-850: reproductive performance study in rats treated continuously through two successive generations", Life Science Research Limited, Eye, Suffolk, England, 10 July 1989. LSR Report No. 89/0901. CD rats, 24/sex/group, were dosed in diet with fenpyroximate (formerly NNI-850), purity 97.3%, at 0, 10, 30, or 100 ppm throughout the study. Pre-mating periods lasted 14 weeks: one littering period per generation. Estimated achieved pre-mating dose levels were 0.67, 1.99, and 6.59 mg/kg/day in F0 males, 0.83, 2.44, and 8.60 mg/kg/day in F0 females, 0.78, 2.33, and 8.45 mg/kg/day in F1 males, and 0.96, 2.82, and 9.92 mg/kg/day in F1 females. Parental NOEL = 30 ppm (marked body weight decrements in F0 and F1 males, lesser change in corresponding females: modest food consumption decrements in males - statistically significant in F0 males only). Reproductive NOEL = 100 ppm (no changes in reproductive indices). Progeny NOEL = 30 ppm (marked body weight gain decrements after lactation day 14 in both generations).

Study is acceptable, with no adverse effects. Aldous, 7/19/01.

TERATOLOGY, RAT

****52876-027 179637** Higgins, C., “NNI-850: Teratology study in the rat”, Life Science Research Limited, Eye, Suffolk, England, 2/9/89. Report No. 89/0722. Twenty-two CD rats/group were dosed by gavage with 0, 1, 5, or 25 mg/kg/day Fenpyroximate (97.6% purity) in 1 % aq. CMC containing 0.1% Tween 80 (10 ml/kg) during gestation days 6-15 of a standard developmental study. Maternal NOEL = 5 mg/kg/day (decreased food consumption, associated with decreased body weight). Developmental NOEL = 25 mg/kg/day (highest dose tested). High dose fetuses had an increased incidence of uni/bilateral or bilateral 13th thoracic ribs compared to concurrent controls. This does not appear to be treatment-related, since this study showed little dose-response, and since high dose incidences were typical of contemporary incidences of the sub-group of rats utilized in this study. Study is acceptable, with no adverse effects. Aldous, 8/7/01.

52876-026 179636 pilot study for 52876-027 179637, above. The pilot study found modest body weight decrements and modest food consumption reductions at 25 mg/kg/day. Thus the selected high dose level for the primary study was marginally adequate, based on this pilot study. Aldous, 7/26/01 (no worksheet).

52876-027 179638 Supplemental data relating to the two main developmental toxicity studies. Issues relating to the rat study were (1) evidences of maternal toxicity, and (2) detailed historical control data for 13th rib incidence in the subcolony of rats from which the primary study animals were taken. Data are incorporated in the review of the primary study.

TERATOLOGY, RABBIT

****52876-029 179640** King, V. C., “NNI-850: Teratology study in the rabbit”, Life Science Research Limited, Eye, Suffolk, England, 2/14/89. Report No. 89/NHH051/0687. Fifteen NZW rabbits/group were dosed by gavage (in 1 % aq. CMC containing 0.1% Tween 80) with 0, 1.0, 2.5, or 5.0 mg/kg/day fenpyroximate (97.6% purity) during gestation days 6-19. Maternal NOEL = 1 mg/kg/day (total litter losses for one doe at each of dose levels 2.5 and 5.0 mg/kg/day). Developmental NOEL = 2.5 mg/kg/day (slightly increased incidences of “slightly folded retina” in 5.0 mg/kg/day fetuses). Both of the above findings are equivocal treatment effects. A more definitive evidence of a maternal toxicity effect is the consistent increase in incidence of “few feces in undertray” at 5 mg/kg/day over the course of the dosing period. Modest decrements in body weight and food consumption at 5 mg/kg/day may be considered as supplemental evidence of a treatment effect at that dose level. Record 52876-027 179638 notes that the apparent “folded retina” effect is a common artifact of tissue preparation in Bouin’s solution. Acceptable. Aldous, 8/7/01.

52876-027 179638 Supplemental data relating to the two main developmental toxicity studies. Issues relating to the rabbit study were (1) evidences of maternal toxicity, and (2) evidences that the apparent

“folded retina” effect was incidental. Items were considered in review of the primary rabbit study (see worksheet for primary study).

52876-028 179639 “NNI-850: Preliminary teratology study in the rabbit”. A pilot rabbit teratology study with a maximal dose level of 5 mg/kg/day fenpyroximate. This pilot study provided marginal evidence that 5 mg/kg/day was a sufficiently challenging dose for the primary study. Findings are discussed briefly in review of the primary study (52876-029 179640). Aldous, 7/11/01 (no separate worksheet for this record).

52876-031 179642 “NNI-850: Tolerance study in the rabbit”. This study involved 4 NZW female rabbits. The first two rabbits (Test 1) were non-pregnant. These were treated in a “staircase” dosing pattern, in rabbits received 10 mg/kg/day fenpyroximate for 2 days, 20 mg/kg/day for the next two days, and 40 mg/kg/day for the final treatment day. These animals lost an average of 105 g body weight at the end of the 10 mg/kg/day treatments, an additional 125 g at the end of the 20 mg/kg/day treatments, and an additional 160 g after one day at 40 mg/kg. One of these rabbits had reduced fecal output beginning with the 20 mg/kg/day dosing period. The other had scouring (diarrhea) beginning during the 10 mg/kg/day treatments and reduced fecal output at 40 mg/kg. In Test 2, the other 2 rabbits were maintained at 10 mg/kg/day from days 6-13 of gestation. These rabbits lost 80 g and 310 g of body weight between days 6 and 13. Both rabbits were noted to have had reduced food intake and reduced fecal output during at least the last 4 days of the study. Although limited in scope, these studies suggest that 10 mg/kg/day would be excessive for use in a teratology study. Aldous, 7/12/01 (no worksheet).

52876-030 179641 “Upgrading request for MRID 43429504 Guideline 83-3(b): Developmental toxicity in the rabbit”. This record contains clarification of clinical signs data from the primary teratology study [Record No. 179640] on fenpyroximate, specifically findings of “few feces in undertrays”. The original report indicated a high dose effect on this subject, based on [rabbit-days with “few feces” sign]/[total rabbit days], including only rabbits carrying viable fetuses at term. The new information shows the total percentage of rabbits affected per group and numbers of rabbits with the “few feces” sign on any given day of the study. Also, this record gives further information on fetal “folded retina”: historical control incidences and incidence data per litter in the primary fenpyroximate teratology study. These data are incorporated into the review of the primary study. Aldous, 7/12/01 [no separate worksheet for this record: essential data are included in the review of the primary teratology study].

GENE MUTATION

** 52876 – 037 179648 May, K. “NNI-850 (technical grade): Assessment of mutagenic potential in amino-acid auxotrophs of *Salmonella typhimurium* and *Escherichia coli* (The Ames Test), amended final report.” (Life Science Research Limited, Suffolk, UK, LSR Report No. 89/NHH039/1010, final date of 6/13/88, amended final report, 12/4/89) NNI-850 (lot 013, technical grade, 97.3%) was tested with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 plus *Escherichia coli* WP2 uvrA tryptophan mutant at concentrations of 0 (DMSO), 50, 158, 500, 1580 and 5000 µg/plate, with and without rat liver activation, in triplicate, incubated 48 hours, with two trials. At 5000 µg/plate, there was a thinning of the background lawn in TA98,

TA1538, TA1537 and WP2 uvrA strains. There was no evidence of an increase in revertants in any strain. Positive controls were functional. **Acceptable.** (Gee, 8/13/01)

** 52876 – 038 179649 Hodson-Walker, G. “NNI-850: Investigation of mutagenic activity at the HGPRT locus in a Chinese hamster V79 cell mutation system.” (Life Science Research Limited, UK, LSR Report No. 89/NHH042/1060, final report date, 1/18/89; amended report, 12/4/89) NNI-850 (lot no. 013, technical grade, 97.3%) was tested for the induction of mutations with Chinese hamster V79 cells, 4 – 1 clone 9 3/12, at concentrations of 0 (acetone), 3, 10, 30, 100 and 330 µg/ml (the maximum practical concentration), with exposure for 3 hours in the presence and absence of rat liver S-9 activation. There were duplicate cultures per concentration, with triplicate plates for cell survival immediately after treatment and for plating efficiency and mutation frequency after the 7-day expression period. Two trials were conducted. Resistance to 6-thioguanine was used to determine the mutation frequency. Positive controls were ethylmethanesulfonate (- S-9) and 7, 12-dimethylbenzanthracene (+ S-9). There was no cytotoxicity at 330 µg/ml. There was no consistent increase in mutation frequency with treatment; the positive controls were functional. **Acceptable.** (Gee, 8/13/01)

CHROMOSOME EFFECTS

** 52876 – 039 179650 Hodson-Walker, G. “NNI-850: Assessment of clastogenic action on bone marrow erythrocytes in the micronucleus test: second amended report.” (Life Science Research Limited, Suffolk, UK, LSR Report No. 89/NHH041/1059, Final Report: 8/4/88; first amended report: 8/25/89; second amended report: 12/4/89) NNI-850, technical grade (lot 013, 97.3%) was given by oral gavage in a single dose at 0 (0.5% methylcellulose), 80, 400 or 2000 mg/kg, 15 ml/kg, to CD-1 mice. Five per sex were terminated at 24 hours at each dose, including the positive control of chlorambucil. At 48 and 72 hours after dosing, 5/sex for controls and 2000 mg/kg were terminated. Micronuclei in the bone marrow were scored for polychromatic and mature erythrocytes and the ratio of the cell types determined from 2000 erythrocytes per animal. At 2000 mg/kg, clinical signs of piloerection, lethargy, paraplegia and body weight loss were reported. No signs were noted at 80 or 400 mg/kg. NOEL = 400 mg/kg. There was no indication for the formation of micronuclei as a result of exposure at doses up to 2000 mg/kg. There was an indication of bone marrow toxicity from the decrease in the ratio of polychromatic:mature erythrocytes at the high dose. The positive control was functional. **Acceptable.** (Gee, 8/13/01)

** 52876 – 040 179651 Hodson-Walker, G. “*In vitro* assessment of the clastogenic activity of NNI-850 in cultured human lymphocytes, third amended report.” (Life Science Research Limited, Suffolk, UK, LSR Report No. 89/NHH040/1058, final report, 11/14/88; first amended report, 12/8/88; second amended report, 8/25/89; third amended report, 12/4/89) NNI-850 (technical grade, lot 013, 97.3%) was tested for the formation of chromosomal aberrations with human lymphocytes in culture. Whole blood was obtained from a male volunteer, placed into culture with phytohemagglutinin for 48 hours, then exposed to NNI-850 at concentrations of 0 (acetone), 1.25, 5 or 20 µg/ml, for 2 hours with and without activation with rat liver S-9. Following the two hours, cells were washed, resuspended in complete medium, and the test solutions added at the original concentrations for an additional 22 hours of exposure without S9 activation. Colcemid was added for the last 3 hours of the incubation. There were triplicate cultures per group. Negative control was untreated, positive controls were chlorambucil for minus S9 and cyclophosphamide with activation. A single trial was

conducted. Mitotic indices were determined by counting approximately 1000 lymphocytes per culture. For chromosomal aberrations, 100 cells per culture were scored. Results were reported as % cells with aberrations including and excluding gaps. The mitotic indices for the treated groups were lower than the vehicle and negative controls. Excluding gaps, there was no indication of a treatment-induced increase in chromosomal aberrations under the study conditions. **Acceptable** with minor deviations (single volunteer, continued treatment over 22 additional hours). (Gee, 8/14/01)

DNA DAMAGE

** 52876 – 041 179652 Haworth, S. R.; M. A. Cifone, Study Director “Mutagenicity test on NNI-850, technical grade, in the rat primary hepatocyte unscheduled DNA synthesis assay.” (Hazleton Laboratories America, Inc., Kensington, MD, Study no. 10753-0-447, 12/4/89) NNI-850 (technical grade, lot 013, 97.3%) was assayed for the induction of unscheduled DNA synthesis with primary rat hepatocytes isolated from a male Fischer 344/NHsdBR rat. Fifteen concentrations ranging from 0.005 to 255 µg/ml were used, dissolved in DMSO. The exposure was 18.1 hours, followed by processing. Concentrations of 0 (DMSO), 0.25, 0.51, 0.102, 0.255, 0.509 and 1.02 µg/ml were analyzed. Higher concentrations were too toxic for analysis. Survival at 0.509 was 83.8% and at 1.02, 78.8%. No data were included for higher concentrations. 2-Acetylaminofluorene was the positive control. UDS was determined by autoradiography with incorporation of ³H-thymidine. From the net nuclear grain counts, exposure to NNI-850 under the conditions of the assay did not induce UDS. The positive control was effective. **Acceptable**. (Gee, 8/15/01)

52876 – 042 179653 Watanabe, M. “Mutagenicity test on NNI-850, technical grade, DNA repair test (Rec-assay).” (Kodaira Laboratories, Tokyo, Japan, Study 88-0072, 10/31/88) NNI-850 (lot 013, 97.3%, technical grade) was tested with *Bacillus subtilis* strains H17 (rec⁺) and M45 (rec⁻) by the disk assay. Exposures were: 0 (DMSO), 10, 20, 50, 100, 200 and 500 µg/disk applied to a plate containing agar and bacteria. The highest amount tested was limited by the solubility in DMSO (28.5 mg/ml) and a 20 µl/disk volume. NNI-850 was tested with and without rat liver activation, overnight incubation. Kanamycin was used as a negative control; mitomycin C and 2-aminoanthracene were positive controls without and with activation, respectively. Controls were functional. There was no inhibition of growth for either strain with exposure to NNI-850, indicating no cytotoxicity at the highest level tested and no differential growth, indicating DNA damage/repair. The study was negative under the test conditions. The study was **unacceptable** (a single plate per exposure condition). **Not upgradeable**. (Gee, 8/15/01)

NEUROTOXICITY

019; 179629; “NNI-850: Acute Delayed Neurotoxicity Study in the Hen” (Cummins, H.A., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 89/NHH054/0686, 1/4/90). 817. NNI-850 Technical (Lot/Batch No. 025, purity = 97.0%), suspended in 0.5% w/v methylcellulose in distilled water, was administered by gavage to 12 Sterling Ranger hybrid hens at a dose level of 5000 mg/kg on Day 1 and on Day 22. 6 hens treated with vehicle only and 6 hens treated with 600 mg/kg of TOCP were also included in the study. 5/6 TOCP treated hens were sacrificed *in extremis* between Day 21 and Day 39; no other mortalities occurred. No clinical signs were observed in the 12 animals treated with test material or in the animals treated with vehicle only. Ataxia was observed in the TOCP

treated animals beginning on Day 15. Histopathological examination revealed no treatment-related pathology. NOEL (F) = 5000 mg/kg (based on the absence of ataxia in test material treated animals). **Acceptable.** (Corlett, 6/8/01)

METABOLISM

Metabolism studies contained in Document Nos. 52876-043 to 52876-045 were sent as parts of a single package. 52876-043 is a pharmacokinetics study using [Pyrazole-¹⁴C] NNI-850. 52876-044 is metabolism and disposition study on [Pyrazole-¹⁴C] NNI-850, whereas 52876-045 is the parallel metabolism and disposition study on [Benzyl-¹⁴C] NNI-850. No individual study nor the collective studies adequately address the data requirements for rat metabolism. Two dose levels were used in all studies: 2 and 400 mg/kg. The former is well-suited for a low dose level, however the latter proved to be such a disturbance to digestive system function as to be impracticable for future studies. The review of 52876-045 179657 (below) gives the most complete detail of the deficiencies which apply to this package of studies. The essential features of an acceptable metabolism study would be satisfied if the registrant were to perform an additional gavage exposure study using [Pyrazole-¹⁴C] NNI-850 at the low dose level (2 mg/kg) in small numbers of male and female rats providing (1) that biliary excretion would be assessed, and (2) that there would be efficient separation and identification of any primary metabolites which constitute 5% or more of the total label in fecal or urinary excretion products. Aldous, 9/6/01.

52876-044 179656 Sharp, D. E., "Metabolism and disposition of [Pyrazole-¹⁴C] NNI-850 in rats", Hazleton Laboratories America, Inc., Madison, WI., 5/16/91 Report No. HLA 6283-102. In a preliminary phase of the present study, two rats/sex were treated with a single oral dose of 2 mg/kg [Pyrazole-¹⁴C] NNI-850 (99.6% chemical purity), prior to collection of urine, feces, organic volatiles, and carbon dioxide. The preliminary study found no detectable carbon dioxide, and organic volatiles were either non-detectable or below quantifiable levels. In either sex, most label was recoverable in excreta, with feces predominating about 2 to 3-fold over urine as the primary route. Most of the label from feces and urine was collected within 24 hours, with residues being quite diminished after 48 hours. The definitive study used at least 3 rats/sex per dose/time interval combination. Single oral doses were low (2 mg/kg) or high (400 mg/kg). Sacrifice time intervals after radiolabeled NNI-850 treatment were 12, 24, and 168 hr for low dose groups, and 12, 24, 96, 120, and 168 hr for high dose groups. Repeat dose groups received 2 mg/kg/day unlabeled NNI-850 for 14 days, followed by a single treatment with labeled NNI-850 at 2 mg/kg. This group was maintained for 168 hr before sacrifice. All 168-hr groups consisted of 5/sex, and these were used for excretion samples at intervals throughout that period. Metabolite identification was performed by comparisons of 2-dimensional TLC mobilities of excreta extracts with mobilities of a series of proposed metabolites in two sets of solvent systems (i.e. standard chromatograms by visualization under UV light were compared to autoradiograms of fecal or urinary extracts). There was no confirmation of structures of co-eluting spots by other means such as NMR or MS. All treatment groups were used for tissue residues at sacrifice. Total fecal and urinary outputs did not vary systematically between low dose, high dose, and repeat low-dose regimens: average percentage values were 79 and 75% (feces, M & F) and 15 and 20% (urine, M & F). **Feces analyses:** High dose fenpyroximate administration led to slowed transit of radiolabel through the alimentary tract, and about 80% of fecal excretion was parent compound, suggesting poor absorption.

A single 2 mg/kg dose found about 8% of fecal metabolites as parent compound, about 13% presumed to be the ester hydrolysis product, with other characterized metabolites accounting for about 5% or less of fecal radioactivity. Uncharacterized metabolites which remained at the origin of the 0-24 hr TLC plates of 2 mg/kg groups constituted 47-50% of fecal label, compared to 2-4% in 400 mg/kg groups, suggesting that most of the dose was absorbed and metabolized following low dose administration. No reported attempt was made to identify fecal extract spots at or near to the origin by alternate methods. Additional spots (not on the origin), some comprising 5-10% of fecal radioactivity, were also not characterized. The major identified **urinary** metabolite was evidently 1,3-dimethyl-5-phenoxy-pyrazol-4-carboxylic acid. This compound, designated M-8, was substantially conjugated as a glucuronide.

The study is unacceptable and not upgradeable. As noted, this study found that most of the radiolabel resided in feces, but no biliary cannulation study was undertaken to more definitively address the degree of absorption. This a serious deficiency in the study, and a biliary cannulation component should be present in the replacement study. As noted above, structures of presumed metabolites were not confirmed by such as NMR or MS. Quantitatively important fecal metabolites were not further characterized, including many which did not migrate far from the origin in the TLC systems used. Aldous, 8/28/01.

52876-045 179657 Sharp, D. E., "Metabolism and disposition of [Benzyl-¹⁴C] NNI-850 in rats," Hazleton Laboratories America, Inc. (Madison, WI), 5/16/91. Report No. HLA 6283-101. This study is parallel to 52876-045 179656 (same author, facility, and completion date). The design of this study is virtually identical to the above (see that 1-liner for methods). A pilot study using [Benzyl-¹⁴C] NNI-850 found no measurable label in exhaled organic volatiles or CO₂, hence exhaled air was not further studied. This study provided a few usable elements of information: (1) elimination was predominantly in feces and to a much lesser extent in urine, regardless of dose level, (2) most elimination in urine or feces was complete within 24-48 hours except in the high dose (400 mg/kg) group, in which progress through the alimentary tract and elimination were protracted to at least 5-7 days, (3) parent compound accounted for about 10% of fecal elimination at 2 mg/kg, and about 89% of fecal elimination at 400 mg/kg, hence high dose exposure led to very poor absorption, whereas low dose exposure evidently led to appreciable uptake, (4) significant metabolites in feces were evidently oxidation products of the tert-butyl benzoate moiety to form carboxylic acid residues, and (5) a substantial portion of label in urinary metabolites may have been terephthalic acid. This study is **unacceptable and not upgradeable**, for the same reasons as the parallel Record No. 179656: (1) no biliary cannulation study was undertaken, despite demonstration that main route was fecal excretion, leaving great uncertainty as to the amount of label absorbed from the alimentary tract, (2) determination of metabolites was made almost solely on co-elution with radiolabeled standards in two 2-dimensional TLC systems, with quantitation by autoradiography: there was no definitive testing of fractions by NMR or MS to assess structure, (3) some metabolites, especially those which did not migrate far from the origin in the TLC systems used, were not further characterized, even though these represented substantial portions of fecal or urinary radioactivity, (4) in at least one case, it was unclear why investigators could not distinguish between metabolites having fundamentally different structures, particularly since it appeared that one solvent system could separate these spots quite efficiently. A new study is needed. Aldous, 8/28/01.

52876-043 179655 Sharp, D. E., "Metabolism and disposition of [Pyrazole-¹⁴C] NNI-850 in rats" and "Metabolism and disposition of [Benzyl-¹⁴C] NNI-850 in rats", Hazleton Laboratories America,

Inc. (Madison, WI), 12/7/90 (for both reports). Report Nos. HLA 6283-104 and -103, respectively. Both studies used five rats/sex/group, dosed with 2 or 400 mg/kg [Pyrazole-¹⁴C] NNI-850 or [Benzyl-¹⁴C] NNI-850 by gavage in 1% aqueous Tween® 80. Tail vein blood was collected at intervals for 7 days. **Pyrazole-¹⁴C Study:** Half-lives in blood were 8.9 hr for both M and F at 2 mg/kg. Times to maximum concentration in blood radioactivity were 11.0 and 11.4 hr for M and F at 2 mg/kg. By 72 hr, blood levels reached or approached limits of detection. In contrast, 400 mg/kg led to half-lives in blood of 49 and 45 hr for M and F. Times to maximum concentration in blood radioactivity of these high dose rats were 101 and 90 hr for M and F. It took from 168 to 216 hrs to achieve non-detectable levels in blood of 400 mg/kg rats. **Benzyl-¹⁴C Study:** Half-lives in blood were 6.1 hr and 7.9 hr for M and F, respectively, at 2 mg/kg. Times to maximum concentration in blood radioactivity were 7.8 and 7.2 hr for M and F at 2 mg/kg. By 48 hr, blood levels reached or approached limits of detection. In contrast, 400 mg/kg led to half-lives in blood of 47 and 35 hr for M and F. Times to maximum concentration in blood radioactivity of these high dose rats were 29 and 86 hr for M and F. It took 168 hrs to approach or achieve non-detectable levels in blood of 400 mg/kg rats. Useful supplemental data. Aldous, 8/29/01.

SUBCHRONIC STUDIES

(90-day feeding study)

020; 179630; “NNI-850: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks” (Aughton, P., Life Science Research Ltd., Eye, Suffolk, England, LSR Report No. 89/NHH021/0972, 12/4/89). 821. NNI-850 (Lot No. 002, purity = 97.8%) was admixed to the diet at dose levels of 0 (untreated diet only), 20, 100, or 500 ppm (for males, 0, 1.30, 6.57, and 35.22 mg/kg/day, respectively, and for females, 0, 1.65, 8.29, and 38.60 mg/kg/day, respectively) and fed continuously to 10 CD rats per sex per dose for 13 weeks. No treatment-related mortalities occurred. A treatment-related decrease in mean body weight was observed in both sexes at 100 and 500 ppm. Treatment-related increases in mean red blood cell, hemoglobin, and hematocrit levels in both sexes were observed at 500 ppm. Microscopic examination revealed incidences of hepatocytic hypertrophy in both sexes at 100 and 500 ppm. **No adverse effects.** NOEL (M)= 1.30 mg/kg/day (20 ppm) and NOEL (F)= 1.65 mg/kg/day (20 ppm) based on decreased mean body weight and incidences of hepatocytic hypertrophy. **Acceptable.** (Corlett, 6/18/01)

021; 179631; “NNI-850: Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 13 Weeks” (Broadmeadow, A., Life Science Research Ltd., Eye, Suffolk, England, LSR Report No. 89/NHH036/1111, 12/20/89). 821. NNI-850 Technical (Lot No. 014, purity = 98.4%) was administered to 4 pure-bred beagle dogs per sex per dose in gelatin capsules once a day 7 days a week for 13 weeks at dose levels of 0 (empty capsules), 2, 10, or 50 mg/kg/day. 2 female animals at 50 mg/kg/day *in extremis* were sacrificed. A treatment-related decrease in mean body weight gain was observed in both sexes at 50 mg/kg/day. Microscopic examination conducted on the animals sacrificed revealed fine vacuolation of medullary rays in the kidneys and glycogen depletion in the liver. **No adverse effects.** NOEL (M/F) < 2 mg/kg/day based on treatment-related diarrhea **Acceptable.** (Corlett, 6/25/01)

(Dermal)

024; 179634; “21-Day Repeated-Dose Dermal Toxicity Study of Fenpyroximate in the Rat”

(Wilkinson, G.E. et al., Battelle Columbus Operations, Columbus, OH, Battelle Study Number SC920009, 7/13/92). Fenpyroximate (Identity Code NNI-850, Lot No. 1AA0002L, purity = 99%), moistened with deionized water, was applied to the clipped skin of 5 Sprague-Dawley rats per sex per dose at dose levels of 0 (sham-treated), 100, 300, and 1000 mg/kg/day for 6 hours per day for 21 consecutive days using an elastic wrap. No animals died. Clinical observations revealed no treatment-related signs of systemic toxicity and no signs of dermal irritation. Treatment-related decreases in mean body weight and food consumption were observed in both sexes at 1000 mg/kg/day. Microscopic examination revealed acanthosis of treated skin at 100, 300 and 1000 mg/kg/day in both sexes. **No adverse effects.** NOEL (M/F, systemic) = 300 mg/kg/day (based on body weight and food consumption data) and NOEL (M/F, skin) < 100 mg/kg/day (based on minimal acanthosis in treated animals). **Acceptable.** (Corlett, 6/28/01)

023; 179633; “21-Day Repeated-Dose Dermal Limit Test of Fenpyroximate in the Rat” (Wilkinson, G.E. et al., Battelle Columbus Operations, Columbus, OH, Battelle Study Number SC910105, 1/6/92). Fenpyroximate (Identity Code NNI-850, Lot No. 1AA0002L, purity = 99.0%), moistened with deionized water, was applied to the clipped skin of 5 Sprague-Dawley rats per sex per dose at dose levels of 0 (sham-treated) and 1.0 g/kg/day for 6 hours per day for 21 consecutive days. No animals died. Clinical observations revealed no signs of systemic toxicity and no signs of dermal irritation. A statistically significant decrease in mean body weight in treated animals of both sexes when compared to untreated animals was observed. Microscopic examination revealed treated skin with minimal acanthosis in the treatment group animals (3/5 males and 4/5 females). NOEL (M/F, systemic) < 1.0 g/kg/day (based on body weight data) and NOEL (M/F, skin) < 1.0 g/kg/day (based on incidences of acanthosis in treated animals). **Supplemental** (only one dose level (1.0 g/kg/day) was used and effects were observed; therefore, no NOEL could be assigned). (Corlett, 6/26/01)

022; 179632; “21-Day Repeated-Dose Dermal Range-Finding Study of Fenpyroximate in the Rat” (Wilkinson et al., Battelle Columbus Operations, Columbus, OH, Battelle Study Number SC910038, 11/6/91). Fenpyroximate (Identity Code NNI-850, Lot No. 1AA0002L, purity = 99.0%) was moistened with deionized water, was applied to the clipped skin of 5 Sprague-Dawley rats per sex at a dose level of 1.0 g/kg/day for 6 hours per day for 21 consecutive days. No animals died. No signs of systemic toxicity and no signs of dermal irritation were observed. NOEL (M/F, systemic, skin) = 1.0 g/kg/day (based on no signs at highest dose tested). **Supplemental** (no untreated test animals were included in the study; none of the following were performed on the test animals: hematology, serum chemistry, organ weight determinations, necropsies, and microscopic examination of tissues). (Corlett, 6/25/01)

(Inhalation)

025; 179635; “A Four Week Nose-Only Inhalation Toxicity Study of NNI-850 in the Rat” (Hoffman, G.M., Bio/dynamics Inc., East Millstone, NJ, Project No. 90-8290, 6/26/91). NNI-850 (Lot No. 90-01, 88.7% a.i.), was administered into the breathing zone as a dust in a nose-only manner to 5 Sprague-Dawley CD[®] rats per sex per dose at dose levels (mean gravimetric concentration) of 0.000025 (air only), 0.0019, 0.01, and 0.05 mg/l/day (mean MMAD (GSD) of 0.82 (1.5), 2.8 (2.2), 3.2 (2.2), and 3.1 (2.1) µm, respectively) with an additional 5 rats per sex per dose at the control and high dose levels

included to test recovery for 2 weeks following dosing. Animals were exposed for 6 hours per day, 5 days per week, for 4 weeks. No animals died. Weekly detailed physical examinations revealed treatment-related dry and moist rales at all dose levels and labored breathing in high-dose animals with signs abating in the high-dose group recovery animals. Microscopic examination on the nasopharyngeal tissue revealed treatment related squamous metaplasia of respiratory mucosa in mid- and high-dose males and high-dose females and atrophy of olfactory mucosa in high-dose males and females; no treatment-related findings were observed in the recovery group animals. **No adverse effects.** NOEL (M/F) < 0.0019 mg/l/day (based on clinical signs). **Supplemental study** (only 5 animals per sex per dose level used, the animals dosed for only 4 weeks, particle size distribution determined only once per week for each dose level, and no ophthalmological examinations conducted). (Corlett, 7/9/01)